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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/577,385	07/03/2006	Hanspeter Mettler	LP-2016	4705
217	7590	03/22/2010	EXAMINER	
FISHER, CHRISTEN & SABOL P.O. Box 18385 WASHINGTON, DC 20036				PIHONAK, SARAH
ART UNIT		PAPER NUMBER		
1627				
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03/22/2010		PAPER		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/577,385	METTLER, HANSPETER	
	Examiner	Art Unit	
	SARAH PIHONAK	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 10 March 2010.
 2a) This action is FINAL. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-24 is/are pending in the application.
 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) 1-24 is/are rejected.
 7) Claim(s) _____ is/are objected to.
 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ . |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ . | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| | 6) <input type="checkbox"/> Other: _____ . |

DETAILED ACTION

This application, filed on 7/3/2006, is a national stage entry of PCT/EP04/11971, filed on 10/22/2004.

Priority

This application claims foreign priority to Application No. 03024865.2, filed on 10/31/2003.

Response to Remarks

1. In a telephone conversation with the Applicant's attorney, Virgil Marsh, on 3/9/2010, it was brought to the examiner's attention that the primary reference previously used for the final office action dated 12/9/2009 had a later filing date than the priority date of the instant application. Therefore, the finality of the previous office action is withdrawn, and a new rejection has been made. The rejection is made in reference to Duprat de Paule et. al., WO 03/029259, which is a French language equivalent of US Patent No. 6,878,665, which was improperly referenced in the previous rejection. This rejection is made regarding the most recent amended set of claims, filed on 11/19/2009.

This action is **NON-FINAL**.

2. Claims 1-24 were examined.
3. Claims 1-24 are rejected.

Claim Rejections-35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148

USPQ 459 (1966), that are applied for establishing a background for determining

obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. Claims 1-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over

Duprat de Paule et. al., WO 03/029259 publication, in view of Saito et. al., EP Patent

Publication No. 1176135 (previously of record). The WO 03/029259 publication is in the

French language. For convenience, the English language equivalent of this publication

(from the U.S. national stage entry), US Patent No. 6,878,665, will be referenced for this

rejection. The WO 03/029259 publication was submitted by the Applicant on the IDS

(filed 4/26/2006).

7. The claims are drawn to a process of preparing an enantiomerically pure (R) or

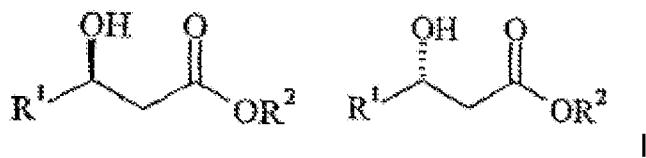
(S) 4-halo-3-hydroxybutyrate of the formula I, with an enantiomeric excess (ee) between

93.2 to 98.1 %, or greater than 90%, for claim 24. The enantiomerically pure 4-halo-

hydroxybutyrate compounds are prepared by selective hydrogenation of a compound of

formula II with a ruthenium complex comprising the chiral Fluoxphos ligand. The

compounds of formula I are shown below:



Where $R^1=CH_2X$, CHX_2 , or CX_3 ; $X=Cl$ or Br ; $R^2=C_{1-4}$ alkyl, C_{3-6} cycloalkyl, aryl, or aralkyl, each optionally substituted with one or more C_{1-4} alkyl groups or halogen atoms.

Duprat de Paule et. al. teaches a ruthenium catalyst for the asymmetric hydrogenation of keto-butyrate compounds, in which the catalyst comprises the Fluoxphos ligand (column 26, claim 11; column 25, claim 9; pp. 10-12, Table 1 reactants). Duprat de Paule et. al. teaches that the keto-butyrate compounds are selectively hydrogenated to form 3-hydroxybutyrate compounds (pp. 10-12, Table 1; column 26, claim 16). The enantiomeric excess of the synthesized alcohols is taught as being greater than 99 %, for some 3-hydroxybutyrate compounds (pp. 10-12, Table 1). It is taught that the ruthenium catalyst complex comprising the Fluoxphos ligand further comprises an alkene (p. 5, column 7, line 54), arene (p. 5, column 8, line 8), diene (p. 9, column 16, lines 60-65), and/or a polar solvent molecule (p. 5, column 7, line 55). It is also taught that the ruthenium-Fluoxphos complex comprises a ligand such as 1,5-cyclooctadiene (p. 9, column 16, lines 60-65) or p-cymene (p. 5, column 8, line 8). Duprat de Paule et. al. also teaches that the catalytic hydrogenation is performed in solvents such as C_{1-4} alcohols (p. 5, column 8, lines 59-60), dimethylformamide (p. 5, column 8, line 57), and further solvent additives, such as acid (p. 9, column 16, lines 60-65). It is also taught that the counterion of the ruthenium complex is Cl^- , Br^- , I^- , BF_4^- , ClO_4^- , or PF_6^- (p. 5, column 8, lines 8-10). The preparation of the ruthenium complex by

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mixing [Ru₂Cl₄(benzene)₂] with the Fluoxphos ligand in a polar solvent such as tetrahydrofuran (p. 9, column 16, lines 10-17) is taught, and that the p-cymene ligand can be substituted for benzene (p. 5, column 8, line 8). The hydrogenation is performed with the hydrogen pressure range between 1 to 150 bar (p. 6, column 9, lines 16-17).

While Duprat de Paule et. al. teaches that the ruthenium-Fluoxphos catalyst is used successfully in preparing a wide variety of selectively hydrogenated alcohols with a high percent ee, such as greater than 99%, it is not explicitly taught that 4-chloro- or 4-bromo-3-hydroxybutyrates can be prepared with an ee value greater than 90%, or between 93.2 to 98.1 %.

Saito et. al. teaches that the ruthenium-SEGPHOS catalyst is effective in catalyzing asymmetric hydrogenations, such as the hydrogenation of ethyl 4-chloroacetoacetate to ethyl (S)-4-chloro-3-hydroxybutanoate (pp. 9-10, example 6; p. 11, claim 1). Regarding the claimed compounds of formula I, ethyl (S)-4-chloro-3-hydroxybutanoate has the substituents defined as follows: R¹=CH₂Cl; X=Cl; R²=ethyl. Particularly, it is taught that ethyl (S)-4-chloro-3-hydroxybutanoate is prepared with an ee of 98.5% (pp. 9-10, example 6). The SEGPHOS ligand taught by Saito et. al. and the Fluoxphos ligand taught by Duprat de Paule et. al. are structurally similar, in that both ligands share the same core structure. The difference between the two ligands is that for Fluoxphos, the bis(difluoromethyldioxy)biphenyl has replaced the bis(methylenedioxy)biphenyl moiety of the SEGPHOS ligand. Duprat et. al. teaches that the ruthenium-Fluoxphos catalyst is effective at preparing a variety of different alcohol compounds, with high enantiomeric selectivity for many. As Saito et. al. teaches that

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ethyl (S)-4-chloro-3-hydroxybutanoate is synthesized with high enantiomeric selectivity with the ruthenium-SEGPHOS ligand, one of ordinary skill in the art would have been motivated, at the time of the invention, to utilize other ruthenium catalysts, such as the structurally similar ruthenium-Fluoxphos catalyst, for the same reaction, because it is taught that ethyl 4-chloroacetoacetate can readily undergo asymmetric hydrogenation to form the alcohol product with high enantiomeric selectivity, and Duprat de Paule et. al. teaches that the ruthenium-Fluoxphos catalyst is effective at selectively hydrogenating a wide variety of compounds to form alcohols of high percent ee. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art, at the time of the invention, to utilize the ruthenium-Fluoxphos catalyst to prepare ethyl (S)-4-chloro-3-hydroxybutanoate with an ee of greater than 90%, because Saito et. al. teaches that the alcohol can be readily prepared with an ee of 98.5 %, and Duprat de Paule et. al. teaches that the ruthenium-Fluoxphos catalyst selectively catalyzes the hydrogenation of a wide spectrum of compounds to form the alcohol products with high percent ee.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARAH PIHONAK whose telephone number is (571)270-7710. The examiner can normally be reached on Monday-Thursday 8:00 AM - 6:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571)272-0629. The fax phone

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number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

S.P.

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1627